REMARKS/ARGUMENTS

Claims 119-123 are pending in this application and are rejected on various grounds. No new claim amendments have been made in this response. Therefore, the listing of claims is identical to that filed in the previous response of September 13, 2005. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §§101 and 112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 for lack of utility allegedly "because they are drawn to an invention with no apparent or disclosed patentable utility." The Examiner maintains that "the instant application does not disclose the biological role of this protein or its significance." Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." Applicants respectfully disagree.

Arguments

In their response filed September 13, 2005, Applicants had submitted that utility for the PRO830 polypeptides and its antibodies is based upon the 2.188 fold to 2.549 -fold gene amplification observed for the DNA encoding PRO830 in lung tumors, which is disclosed in Example 170 of the instant invention. Applicants also submitted a Declaration by Dr. Audrey Goddard which disclosed that this "increase in DNA" of at least 2-fold, in the TaqMan™ PCR gene amplification assay, would be considered significant by one skilled in the art.

However, the Examiner maintains that "the significance can be questioned since eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO830."

In making such a rejection, the Examiner seems to indicate that a tumor marker is patentable only if the marker tests positive in a statistically high number of samples compared to the total number of samples tested or if the tumor tests positive in every tissue type that was studied. However, this is not legally correct. Neither the M.P.E.P. nor the Utility Guidelines require that it is necessary for the Applicant to show a positive result in most or a larger percentage of the tissue samples studied in order to make an assertion of utility, nor are they

needed to show that the tumor marker identifies cancers of various tissues types, *e.g.*: lung, colon, etc. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO830 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Furthermore, as indicated previously, it is well-accepted in the art that not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, even if the association of a tumor marker with a particular type of tumor lesion is rare, or, even if the occurrence of a particular kind of tumor lesion itself is rare, since such markers identify rare tumors, they have great value in tumor diagnosis, and consequently, in tumor prognosis.

The Examiner also says that "neither Livak *et al.*, Heid *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica *et al.* was found to support the rejection." Applicants strongly disagree with such a rejection of the Goddard Declaration.

The above references were cited in the Goddard Declaration that the Applicants filed on September 13, 2005, to show that quantitative TaqMan™ PCR assay is a well-known and widely

used assay in the art for studying gene amplification in various cancers. For instance, the Goddard declaration clearly says that:

> "the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer."

Therefore, Dr. Goddard did not rely on the above mentioned references for determining whether "a 2-fold amplification is significant." These opinions by Goddard were based on Dr. Goddard's own scientific experience and factual findings. So the Examiner has misrepresented the actual purpose for presenting these references in the Goddard Declaration. By making this rejection, the Examiner seems to disregard the expert's opinion based on his/ her own personal disagreement over the significance or meaning of the facts offered, without solid support or scientific showing for her opinion(s). Applicants respectfully remind the Examiner that the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; **it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered**" (Emphasis added). Therefore, barring solid scientific evidence from the art that shows why a 2-fold amplification of DNA in the TaqMan™ PCR assay would not be considered significant by one skilled in the art, the basis for this utility rejection is flawed and is inappropriate.

The Examiner also maintains as before, based on references Doerks *et al.*, Brenner *et al.*, Bork *et al.* that "it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors..."

Applicants once again submit, as was done in the response of September 13, 2005 that their assertion for utility of PRO830 polypeptides is **not** based on structural similarity. Hence, the Examiner has not established a *prima facie* case of lack of utility based on references Doerks

et al., Brenner *et al.*, Bork *et al.* and therefore, this rejection is moot. Instead, as discussed above, utility is based on the results of the gene amplification assay observed for the PRO830 in lung tumors.

The Examiner also contends that "(i)t does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state." The Examiner does **not** find the arguments presented in the response of September 13, 2005 persuasive and repeats the Haynes *et al.*, Pennica *et al.*, Konopka *et al.* and Hu *et al.* citations and alleges that "protein levels couldn't be accurately predicted from the level of the corresponding mRNA transcript and further, to show that "one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increase mRNA of protein levels." Applicants respectfully disagree.

First of all, as discussed above, the increase in PRO830 DNA would not be considered small by one skilled in the art based on the teachings in the Goddard Declaration. As discussed in their previous responses of August 19, 2004 and September 13, 2005 regarding references Pennica and Konopka, Applicants maintain that the above mentioned references cannot be used to establish a poor correlation between mRNA and protein because these references did not show that, in general, it is more likely than not for mRNA and protein levels not to have a correlation. The detailed reasons were clearly discussed in the responses referred to above.

Further, as also discussed previously, the teachings of Haynes *et al.* in fact meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Haynes shows that there was a *general* positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins even though the correlation is "not strictly linear" thereby not enabling one to accurately predict protein levels from mRNA levels. In fact, a careful look at Figure 1 of Haynes indicates that few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, Applicants maintain that contrary to the Examiner's position, the Haynes data actually supports the Polakis' statement that, in general, a positive correlation exists between mRNA and protein levels (even though the correlation may not be linear which prevents the data from being useful for accurately

predicting protein levels from mRNA levels) and that the Examiner's rejection is based on a misrepresentation of the scientific data presented by Haynes *et al.*

In addition, Hu *et al.* did not establish a *prima facie* case for lack of utility as discussed in the responses of July 20, 2004 and September 13, 2005. The Hu *et al.* reference entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added), drew conclusions based upon statistical analysis of information obtained from published literature, and not from experimental data.

The Examiner also bases the utility rejection on the teachings of new references such as Gygi *et al.*, Chen *et al.*, Lian *et al.* and Fessler *et al.* Applicants respectfully submit that none of these references support the Examiner's conclusions that "gene amplification does not necessarily result in increased protein levels."

For instance, Gygi *et al.* did not indicate that a correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). *Accurate prediction* is not a criteria that is necessary for meeting the utility standards. In fact, contrary to the Examiner's statement, similar to Haynes *et al.* (which was cited by the Examiner in the Office Action mailed April 19, 2004), the Gygi data also indicates **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies /cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell (emphasis added). Therefore, high levels of mRNA **generally** correlate with higher levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data, like Haynes *et al.*, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

Nor is the analysis provided by Chen *et al.* applicable to the present application for the following reasons. First of all, Applicants note that the proteins selected for their study in Chen

et al. were identified by staining of 2D gels. As is well known, and was noted in Haynes *et al.* for instance, there are problems with selecting proteins detectable by 2D gels: "It is apparent that without prior enrichment only a relatively small and highly selected population of *long-lived, highly expressed proteins* is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently, it is the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus, Chen *et al.*, by selecting proteins visualized by 2D gels, are likely to have excluded in their analysis many key regulatory proteins which could be candidate cancer markers.

Secondly, the manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Once again, Applicants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II, 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one

isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper which described gene expression of genes in adenocarcinomas and compared that to protein expression. In this paper they report that "these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression." The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma." Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

Accordingly, the data by Haynes, Gygi and Chen confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicants submit that the Examiner's Utility rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.* and Chen *et al.*

Regarding Lian *et al.*, Applicants submit that they only teach that protein expression may not correlate with mRNA level in differentiating myeloid cells and does not teach anything regarding such a lack of correlation for genes in general. In addition, the authors themselves admit that there are a number of problems with the data presented in this reference. At page 520 of this article, the authors explicitly express their concerns by stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and **proteins presented at low level will be missed**. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this **decreased the sensitivity of detection of minor proteins**." (Emphasis added). It is known in the art that Coomassie dye stain is a very insensitive method of measuring protein. This suggests that the authors relied on a very insensitive measurement of the proteins studied. The conclusions based on such measurements can hardly be accurate or generally applicable.

The Examiner also basis this utility rejection on Fessler *et al.*, who examined lipopoysaccharide-activated neutrophilins. Again, as with Lian *et al.*, Fessler *et al.* only examined the expression level of **a few proteins/RNAs** in response to LPS stimulation. Additionally, the PTO has overlooked a number of limitations of the study by Fessler *et al.* For example, as admitted by Fessler *et al.*, protein identification by two-dimensional PAGE limited to well-resolved regions of the gel, may perform less well with hydrophobic and high molecular weight proteins, and tends to select for more abundant protein species (page 31301, col. 1). Harvesting of the LPS-incubated PMNs at 4 hours may have prevented detection of earlier, **transient changes and may have thereby introduced artificial transcript-protein discordance**. Furthermore, the post-LPS incubation, pre-two-dimensional PAGE cell washes **would be expected to remove secreted proteins from further analysis**. In addition, because protein binding of Coomassie Blue has a limited dynamic range and is typically not linear throughout the range of detection, image analysis of Coomassie Blue-stained protein spots should only be consider as semi-quantitative (see page 31301, col. 1). Again, in this study, low abundance proteins were underrepresented. Applicants also note that the proteins in this study "removed secreted proteins from further analysis" while the proteins in the present application are secretory proteins. Therefore, Fessler's study cannot be applied to the present application.

In summary, both Fessler *et al.* and Lian *et al.* have relied on insensitive and inaccurate methods of measuring protein expression levels. The teachings of these two references cannot be relied upon to establish a *prima facie* showing of lack of utility.

Regarding the rejection based on the Wang *et al.* reference to show that, "further action should be taken to characterize the functions of a particular gene of interest, including....validation for the importance of the gene in disease processes," Applicants submit they have already asserted in their response of August 19, 2004 that utility for PRO830 is based on the gene amplification data. That is, they performed the necessary experiments (gene amplification data) to establish utility for PRO830 and have asserted its role as a protein marker to diagnose lung cancer.

For the reasons given above, Applicants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the new references Livak *et al.*,

Heid *et al.*, Gygi *et al.*, Chen *et al.*, Lian *et al.*, Fessler *et al.*, and on previously cited Haynes *et al.*, Pennica *et al.*, Konopka *et al.*, Hu *et al.* and Wang *et al.* either. Therefore, barring evidence to the contrary, utility for PRO830 and its antibodies has been established.

Therefore, Applicants respectfully request that this rejection under 35 U.S.C. §101 and §112, first paragraph, be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C10**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 27, 2006

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